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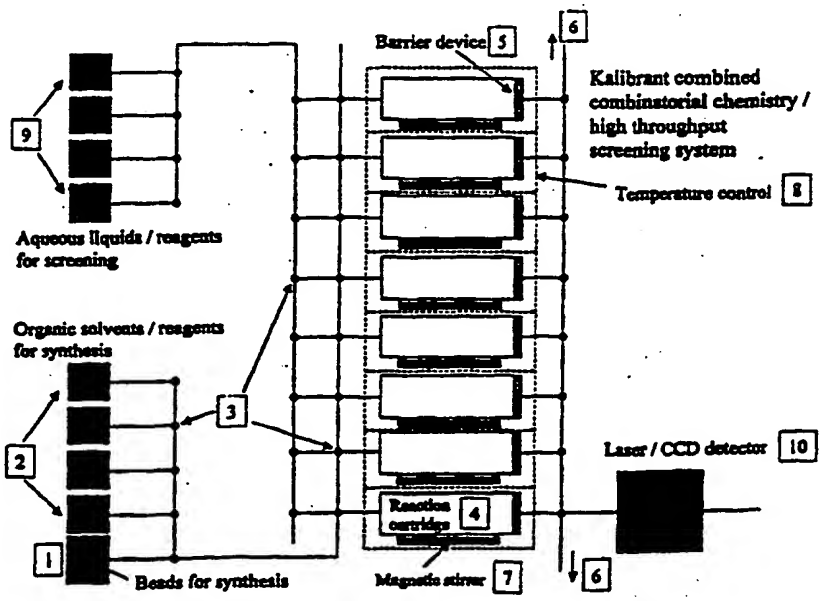
(54) Title: METHOD AND APPARATUS FOR CHEMICAL SYNTHESIS



(57) Abstract

The present invention provides a chemical synthesis apparatus comprising a plurality of reagent inputs (2) and a solid support input (1). Each input (1, 2) is connectable to a main fluid pathway via a respective switchable valve (3). The apparatus further includes a reaction chamber (4) fluidly connectable to the main fluid pathway by a respective switchable valve (3) downstream of the inputs (1, 2). The reaction chamber (4) further includes an outlet downstream of a barrier (5) arranged to prevent passage of said solid supports but allows passage of

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Method and Apparatus for Chemical Synthesis

The present invention relates to a method and apparatus for chemical synthesis. In particular, but not exclusively, the invention relates to a method of and apparatus for combinatorial chemistry for synthesise potential drug candidate molecules.

The process of drug discovery has historically adopted the following development pathway. First, specific molecular targets for drug intervention are defined through in-depth molecular and cellular studies. Once the target is defined, an assay system is developed to monitor biological or kinetic activity of potential drug molecules. Small libraries of chemicals are then synthesised and assayed to select those few that have apparent activity. The biological properties of those selected molecules are then studied on actual cells that are targeted for drug intervention. Those that seem to have favourable biological properties on natural cells then move on to chemical optimisation to improve their potency and selectivity. Their improved biological activity is reconfirmed and, those few that seem to be promising are then moved forward into pre-clinical animal studies to evaluate biological activity *in vivo*.

Combinatorial chemistry represents a novel approach for the synthesis of large collections of compounds for screening. This approach began in the laboratories of peptide chemists for the generation of peptide libraries. Due to the poor oral absorption and metabolic instability of peptides, non-peptide mimetic compounds (usually molecular weight of less than 500) have been developed. In combinatorial chemistry experiments, diverse chemical libraries can be produced by selecting sets of reactants, or building blocks, and reacting the sets with each other in all possible combinations thereby generating hundreds of thousands of individual small molecules. Libraries may consist of molecules free in solution, linked to solid particles or beads, or even arrayed on

surfaces of modified microorganisms. Through the intelligent selection of building blocks, these libraries can be designed either as exploratory libraries, or as targeted libraries that are focused on certain structural hypotheses.

Combinatorial libraries are created in the laboratory by one of two methods, namely split synthesis or parallel synthesis.

In split synthesis, compounds are assembled on the surfaces of microparticles or beads. In each step, beads from previous steps are partitioned into several groups and a new building block is added. The different groups of beads are then recombined and separated once again to form new groups. The next building block is added, and the process continues until the desired combinatorial library has been assembled containing a random selection of molecules. Libraries resulting from split synthesis are characterised by the phrase "one bead, one compound." Each bead in the library holds multiple copies of a single library member.

Combinatorial libraries can also be made by parallel synthesis, in which different compounds are synthesised in separate vessels (without remixing), often in an automated fashion. Unlike split synthesis, which requires a solid support, parallel synthesis can be done either on a solid support or in solution.

Planning and performing combinatorial experiments in the laboratory is a complex and time-consuming process and thus automation is desirable. Instrumentation systems to help speed combinatorial chemistry experiments are believed to be in development at a number of biotechnology and pharmaceutical companies.

WO94/05394 suggests adoption of reusable spatially addressable solid phase plates on which all the synthesis reactions such as deprotection, cleaving and

washing, can take place. US 5,324,483, US 5,593,642, US 5,565,173, US 5,582,801, US 5,567,391 and WO94/08711 disclose the use of reservoir blocks having a plurality of wells for multiple simultaneous synthesis. WO93/12427 discloses the automation of the cleaving, deprotecting and purification processes for solid phase polypeptides. Most of the above processes have been semi-automated with robotic attachments which perform various steps required in synthesis reactions including reagent delivery, changing of reaction/collection vessels, incubation and agitation of reaction mixture, cleavage of synthesised compound from solid support in a range of environments e.g. under pressure or in a vacuum.

US 5,503,805 and WO95/12608 disclose the development of a device for solid phase split and mix chemical synthesis in a closed system. The synthesis is carried out between a parent and daughter reaction vessels. The reagents are transported around the system by flow tubes and valves for example back and forth between the parent and daughter vessels.

The synthesis of organic compounds poses many problems in automated instrumentation including developing a device which will accommodate the wide range of manipulations required for organic synthesis. The synthesis of organic compounds often requires varied conditions such as heating, cooling, agitation, an inert atmosphere etc. Also such synthesis require chemical compatibility between the materials used in the apparatus for synthesis and the solvents and reactants. Therefore the instruments must be constructed of materials which are resistant to organic synthesis conditions and procedures.

The present invention seeks to provide an apparatus for preparing chemicals in an efficient manner.

According to a first aspect of the present invention there is provided a chemical

synthesis apparatus, comprising a plurality of reagent inputs, an input for solid supports and an input for solvents, each input being connectable to a main fluid pathway via a respective switchable valve, the apparatus further including a reaction chamber fluidly connectable to the main fluid pathway by a respective switchable valve downstream of the inputs and the reaction chamber further including an outlet downstream of a barrier arranged to prevent passage of the solid supports but allow passage of unbound molecules. The invention thus provides an apparatus which provides automated production of chemicals without the need for robotic arms for switching trays or the like, as all the manipulations take place in the fluid pathway. It is particularly advantageous for the flow through the reaction chamber to be one way as this allows much greater control of the reaction taking place within the chamber. Versatility is maintained by all of the inputs being connectable to the reaction chamber.

Preferably, the reaction chamber is one of a plurality of reaction chambers, where each reaction chamber is fluidly connectable to the main fluid pathway by a respective switchable valve downstream of the inputs and each reaction chamber further includes an outlet downstream of a barrier arranged to prevent passage of said solid supports but allow passage of unbound molecules. In this way more than one reaction may be undertaken at a time.

It is advantageous if the, some or each of the reaction chambers is removable form the apparatus. Thus physically different reaction chambers, for example with different volumes or internal coatings, can be used in the apparatus depending on the desired reaction.

It is also advantageous if the, some or each reaction chamber includes means for stirring or agitating the contents of the chamber and/or includes temperature control means arranged to control the temperature in the reaction chamber.

In a preferred embodiment of the invention, the output of the, some or each reaction chamber is connectable to detector means. The present invention allows combined synthesis and screening. All the known methods as described above can only be used to carry out synthesis. The device from US 5,565,173 uses solid substrates to carry out the synthesis. The screening or analysis process is carried out separately following the removal of an aliquot of the synthesised compound from the reaction well. In the work disclosed in US 5,324,633 arrays of polymers are also synthesised on a substrate. For the screening process the array of polymers is then exposed to a fluorescently labelled receptor. The fluorescence intensity of the labelled receptor is measured by photon counting using a separate instrument i.e. a confocal microscope. Binding affinities of the receptor for the synthesised polymers are determined through the analysis of the relationship between the fluorescence intensity and the solution concentration of the receptor. A similar procedure has also been described by US 5,639,603, WO95/12608 and US 5,5038,805 involving flow cytometry. The synthesis and screening procedures included numerous steps and separate devices. The devices just described and all the commercially available instruments do not have the combined synthesis/screening capability in the one device. These needs are met by the instrument of the present invention. There is a great benefit in terms of cost and time for having such a device for the screening process following the synthesis stage.

In the combined synthesis and screening apparatus there may be provided a screening agent input fluidly connectable to the respective switching valve for the, some or each of the reaction chambers. Thus the assay can take place in the reaction chamber after, of course, suitable washing cycles. In this case the screening agent input is preferably fluidly connectable to the respective switching valve via a secondary fluid pathway isolated from the main fluid pathway. This is because the synthesis reaction(s) will normally take place in

an organic fluid environment, whereas the screening will normally take place in an aqueous environment.

In order to facilitate different assays a plurality of the screening agent inputs will normally be provided.

The output of the, some of each reaction chamber is advantageously selectively fluidly connectable to an output fluid pathway, the output fluid pathway including valve means to direct the output of the reaction chamber selectively to either a) waste or b) collection and/or analysis of the chemical compound. This simplifies the washing steps which will normally be required.

According to a second aspect of the present invention, there is provided a method of synthesising a chemical compound comprising the steps of:

a) transferring reagents from respective inputs into a reaction chamber via a main fluid pathway, wherein at least one reagent is affixed to a solid support and each of the inputs is separately connectable to the fluid pathway by a respective switchable valve;

b) maintaining the reactants in the reaction chamber to synthesise the chemical compound on the solid support;

c) releasing the chemical compound from the reaction chamber via an output downstream of all of the inputs. Controlled synthesis is thus efficiently and simply provided.

The reagents are advantageously selectively transferred to the reaction chamber. In this way the different reactants are only introduced into the chamber when required.

To increase capacity the reaction chamber in one of a plurality of reaction

chambers all selectively connectable to the main fluid pathway. Normally different compounds are synthesised in different reaction chambers at different times. Alternatively, the same compound is synthesised in more than one reaction chamber and in step b) the reactants are maintained under preselected different reaction conditions in each of the more than one reaction chambers. This allows a way of optimising reaction conditions for a particular reaction.

In most reactions an excess of at least one reactant is used in the synthesis. Advantageously, the method takes place in a closed fluid system which greatly simplifies the control of the reactants, solvents, washing stages, etc..

According to a third aspect of the present invention, there is provided a method of synthesising and screening a chemical compound in a closed fluid system, comprising the steps of:

a) synthesising the chemical compound from reactants in a reaction chamber on a solid support;

b) mixing the chemical compound with a screening agent in the reaction chamber;

c) directing a detectable moiety indicative of the chemical compound to a detector downstream of the reaction chamber.

According to a fourth aspect of the present invention, there is provided a method of synthesising and screening a chemical compound in a closed fluid system, comprising the steps of:

a) synthesising the chemical compound from reactants in a reaction chamber;

b) transferring the chemical compound in a fluid stream to a screening zone where the chemical compound is combined with a screening agent;

c) directing a detectable moiety indicative of the chemical compound to a detector downstream of screening zone.

Both the third and fourth aspects of the invention allow particularly efficient synthesis and screening of new compounds.

A preferred embodiment of the invention will now be described with reference to the accompanying drawings in which:

Fig. 1: shows a schematic representation of an apparatus according to the present invention;

Fig. 2: shows a reaction chamber for use in the apparatus of Fig. 1.

The illustrated and particularly preferred embodiment of the present invention provides a system which can be provided as a combined flow analysis/combinatorial chemistry/high-throughput screening (HTS) device. The individual reactions will be carried out on solid phase supports in sealed reaction vessels. Normally means will be provided for agitation of the vessel or stirring in the vessel to aid mixing. It is possible to vary the reaction conditions/environments (such as temperature, pressure, agitation, etc.) in the different vessels to suit different reactions or to test different conditions for the same reactants.

It is thus possible to directly screen compounds synthesised combinatorially against the multiple targets with the same instrument thereby gaining information on the potential usefulness of the compounds.

Since the preferred embodiment is a synthesising and screening device there is a need to remove all traces of organic solvent (i.e. transfer to an aqueous phase) prior to the screening process of the synthesised compounds with the

targets and receptors.

The device is made up of four main components:

1) Fluid delivery system;
2) Reaction chamber or cartridge;
3) Reagent compartments;
4) Proprietary fluorescence detection system.

Fluid delivery system

The pressurised fluid delivery system is a means of transporting reagent around the system. The fluid delivery system comprises individual components including:

a) flow analysis tubing made of materials such as PTFE or PEEK or any such organic solvent resistant material;
b) switching valves [3] having fluid-contact surfaces made of organic solvent resistant material, which valves divert the flow of solvents, reagents into the appropriate reaction vessels or receptacles;
c) flow sensors which monitor the flow rate within the system;
d) pressure sensors which monitor the pressure within the system.

The fluid delivery system comprises a fluid pathway into which the reactant, solvents etc. can be selectively input. Thereafter the input is delivered to a selected one or more reaction chamber.

Reaction chamber/cartridge

The reaction chamber is the receptacle where the synthesis and screening takes place. The chamber would be made of chemically inert mater such as Teflon, polypropylene, glass etc.. The reaction chamber will normally contain a magnetic flea for stirring of the reagents and will be housed in a sleeve which may include heating and/or cooling elements to effect heating and cooling e.g..

from -40°C to + 150°C as required. A preferred embodiment of a reaction chamber [4] in the form of a removal chamber is shown in Figure 2.

The reaction chamber will selectively receive reactants, solvents, etc. from the main fluid pathway via an inlet. The outlet port of the reaction chamber is separate from the inlet and contains a barrier (e.g. a membrane filter) to prevent the flow of the solid phase beads onto which the combinatorially synthesised compounds are attached when synthesised. The barrier will be formed of a chemically inert material.

Reactions that could be carried out in the chamber include carbon-carbon and carbon-heteratom bond formation reactions e.g. acylation of amines and alcohols, aldol and claisen condensations, cycloadditions, epoxidation, nucleophilic substitutions. Functional group interconversions include mitsunobu reactions, hydroborations, some oxidation reactions, preparations of imines and oximes and esterification/amidations of phosphates and carboxylates.

Reagent compartment

The reagent compartment (1,2) will house the solid phase supports (e.g. beads) which will have the starter building blocks compound attached via a linker. The other building block components and receptor/target molecules used in the screening process will also be contained in normally separate areas of the reagent compartment. Each separate area (1,2) of the housing can separately input the stored component into the fluid delivery system.

The solid phase supports and other building blocks will be suspended or dissolved in a solvent of appropriate density and surface tension. Solid phase supports that could be used in this system include controlled pore glass, silica, latex, polystyrene or similar polymer colloid metal particles.

The preferred and illustrated embodiment provides a combined combinatorial/high throughput screening system. This combined system may be used as an automated parallel combinatorial chemistry synthesiser with the final products released from the beads for storage or otherwise. The system offers a novel approach to lead compound generation with an emphasis on more targeted synthesis and immediate screening of the resulting products. This approach avoids the need to generate vast libraries of compounds which take an enormous length of time to screen and/or take up space waiting to be screened with the resulting concerns over storage stability. The present invention can allow for rapid turnaround of screening results which may lead to structure activity relationships being investigated in almost real time, with subsequent synthesis rounds being led by previous screening results. The ability to fully automate both the synthesis and the screening against multiple targets in a device that is small enough to operate on the bench top means that this approach provides a personal drug discovery platform.

A typical synthesis is described hereinafter where:

The flowlines for delivery of organic solvent are first primed from reagent reservoirs [2] and then a fixed quantity of reaction beads from input [1] are introduced into the flowline through the appropriate switching valve [3] and carried to a first reaction cartridge [4]. The beads are diverted into the reaction cartridge [4] by a first inlet switching valve [3] on the inlet to the cartridge [4] by the barrier device [5] at the outlet. Excess solvent passes through the barrier and is diverted to a waste via a switching valve [3] and output fluid pathway [6]. The first inlet switching valve [3] then diverts flow along the transmission tubing; the process is repeated with reaction beads added to each reaction cartridge as necessary via a respective inlet switching valve [3].

Synthesis in each reaction cartridge then proceeds independently with building

blocks or wash steps added as appropriate from the reagent reservoirs [2] with stirring via stirring means [7] and temperature via temperature control means [8] as necessary. in the illustrated embodiment each individual reaction cartridge [4] has independent temperature control so that the system could also be used during the optimisation experiments, where each cartridge could be used to evaluate changes in solvent, temperature, time, etc..

Following synthesis the beads are washed and then, if required, the product can be cleaved using any of the standard methods and collected by washing out the reaction cartridge via the respective outlet switching valve [3] via the outlet fluid pathway [6]. Although the synthesised product may be directed to the waste point for collection, normally a separate outlet from outlet fluid pathway [6] is provided and the outlet switching valves [3] direct the synthesised product to the designated output.

Alternatively the product may be left on the bead in the cartridge for the on-board automated screening process and after screening detectable compound is output via output fluid pathway [6] to the detector [10].

A typical screening process is described hereinafter:

The flowlines for delivery of aqueous and biological reagents are first primed from the aqueous reservoirs [9], including flushing out the reaction cartridges where necessary. Reagents for the screening assay are transferred to the appropriate cartridges [4] and the synthesised product incubated with the assay reagents. The product can be used on the bead or cleaved prior to incubation when immobilised reagents are used and the target is conjugated to a solid support such as a bead.

Regardless of approach, the screening assay contains a reporter molecule (e.g.

a fluorophore) which at the end of the assay is released through the cartridge and diverted to the laser/CCD detector system [10] via the output fluid pathway [6]. Often the assay will be a fluorescence assay and the amount of fluorescence measured will be related to the degree of inhibition or interference that the product has on the assay.

Details of the detector and assay systems may be found in the Applicants co-pending applications namely WO 97/29376, International Application No. PCT/GB98/02394 and International Application No. PCT/GB98/02396, the disclosures of which are herein incorporated by reference. Please note that the reaction cartridge [4] of the present invention may replace the incubation loops with the barrier [5] on the outlet replacing the of the Applicants previous applications. Alternatively, the synthesised compound may be broken of the bead in the reaction cartridge [4] and transferred to a detector and assayed therein via the outlet fluid pathway [6].

The use of the Applicants multi-analyte detector system means that several screens can be run simultaneously in the same cartridge [4], against the same product.

A separate fluorescent reporter is used for each screen so that a single synthesised product can be examined against a number of different targets at the same time with specific inhibition/interference simultaneously monitored for each target.

CLAIMS:

1. A chemical synthesis apparatus comprising a plurality of reagent inputs, a solid support input, each input being connectable to a main fluid pathway via a respective switchable valve, the apparatus further including a reaction chamber fluidly connectable to the main fluid pathway by a respective switchable valve downstream of the inputs, the reaction chamber further including an outlet downstream of a barrier arranged to prevent passage of said solid supports but allow passage of unbound molecules.

2. The apparatus according to claim 1, wherein the reaction chamber is one of a plurality of reaction chambers, where each reaction chamber is fluidly connectable to the main fluid pathway by a respective switchable valve downstream of the inputs and each reaction chamber further including an outlet downstream of a barrier arranged to prevent passage of said solid supports but allow passage of unbound molecules.

3. The apparatus according to claim 1 or claim 2, wherein the, some or each of the reaction chambers is removable from the apparatus.

4. The apparatus according to any one of the preceding claims, wherein the, some or each reaction chamber includes means for stirring or agitating the contents of the chamber.

5. The apparatus according to any one of the preceding claims, wherein the, some or each reaction chamber includes temperature control means arranged to control the temperature within the reaction chamber.

6. The apparatus according to any one of the preceding claims, wherein the

output of the, some or each reaction chamber is connectable to detector means.

7. The apparatus according to any one of the preceding claims further including a screening agent input fluidly connectable to the respective switching valve for the, some or each of the reaction chambers.

8. The apparatus according to claim 7, wherein the screening agent input is fluidly connectable to the respective switching valve via a secondary fluid pathway isolated from the main fluid pathway.

9. The apparatus according to either claim 7 or claim 8, further including a plurality of the screening agent inputs.

10. The apparatus according to any one of the preceding claims, wherein the output of the, some or each reaction chamber is selectively fluidly connectable to a output fluid pathway, the output fluid pathway including valve means to direct the output of the reaction chamber selectively to either a) waste or b) collection and/or analysis of the chemical compound.

11. A method of synthesising a chemical compound comprising the steps of:

a) transferring reagents from respective inputs into a reaction chamber via a main fluid pathway, wherein at least one reagent is affixed to a solid support and each of the inputs is separately connectable to the fluid pathway by a respective switchable valve;

b) maintaining the reactants in the reaction chamber to synthesise the chemical compound on the solid support;

c) releasing the chemical compound from the reaction chamber via an

output downstream of all of the inputs.

12. The method of claim 11, wherein the reagents are selectively transferred to the reaction chamber.

13. The method of claim 11 or claim 12, wherein the reaction chamber is one of a plurality of reaction chambers all selectively connectable to the main fluid pathway.

14. The method of claim 13, wherein different compounds are synthesised in different reaction chambers at different times.

15. The method of claim 14, wherein the same compound is synthesised in more than one reaction chamber and in step b) the reactants are maintained under preselected different reaction conditions in each of the more than one reaction chambers.

16. The method according to any one of claims 11 to 15, wherein an excess of at least one reactant is used in the synthesis.

17. The method according to any one of claims 11 to 16, wherein the method takes place in a closed fluid system.

18. A method of synthesising and screening a chemical compound in a closed fluid system, comprising the steps of:

a) synthesising the chemical compound from reactants in a reaction chamber on a solid support;

b) mixing the chemical compound with a screening agent in the reaction chamber;

c) directing a detectable moiety indicative of the chemical compound to a detector downstream of the reaction chamber.

19. A method of synthesising and screening a chemical compound in a closed fluid system, comprising the steps of:

a) synthesising the chemical compound from reactants in a reaction chamber;

b) transferring the chemical compound in a fluid stream to a screening zone where the chemical compound is mixed with a screening agent;

c) directing a detectable moiety indicative of the chemical compound to a detector downstream of screening zone.

20. The method of claim 18 or 19, wherein the step a) of synthesising the chemical compound comprises the method of any one of claims 11 to 17.

21. The method of any one of the preceding claims 11 to 17, wherein the method is conducted in the apparatus of any one of claims 1 to 10.

22. The method of any one of the preceding claims 18 to 21, wherein the method is conducted in the apparatus of any one of claims 6 to 10.

23. An apparatus as hereinbefore described with reference to, and as illustrated by, the accompanying drawings.

24. A method of synthesising a chemical compound as hereinbefore described with reference to, and as illustrated by, the accompanying drawings.

25. A method of synthesising and screening a chemical compound hereinbefore described with reference to, and as illustrated by, the accompanying drawings.

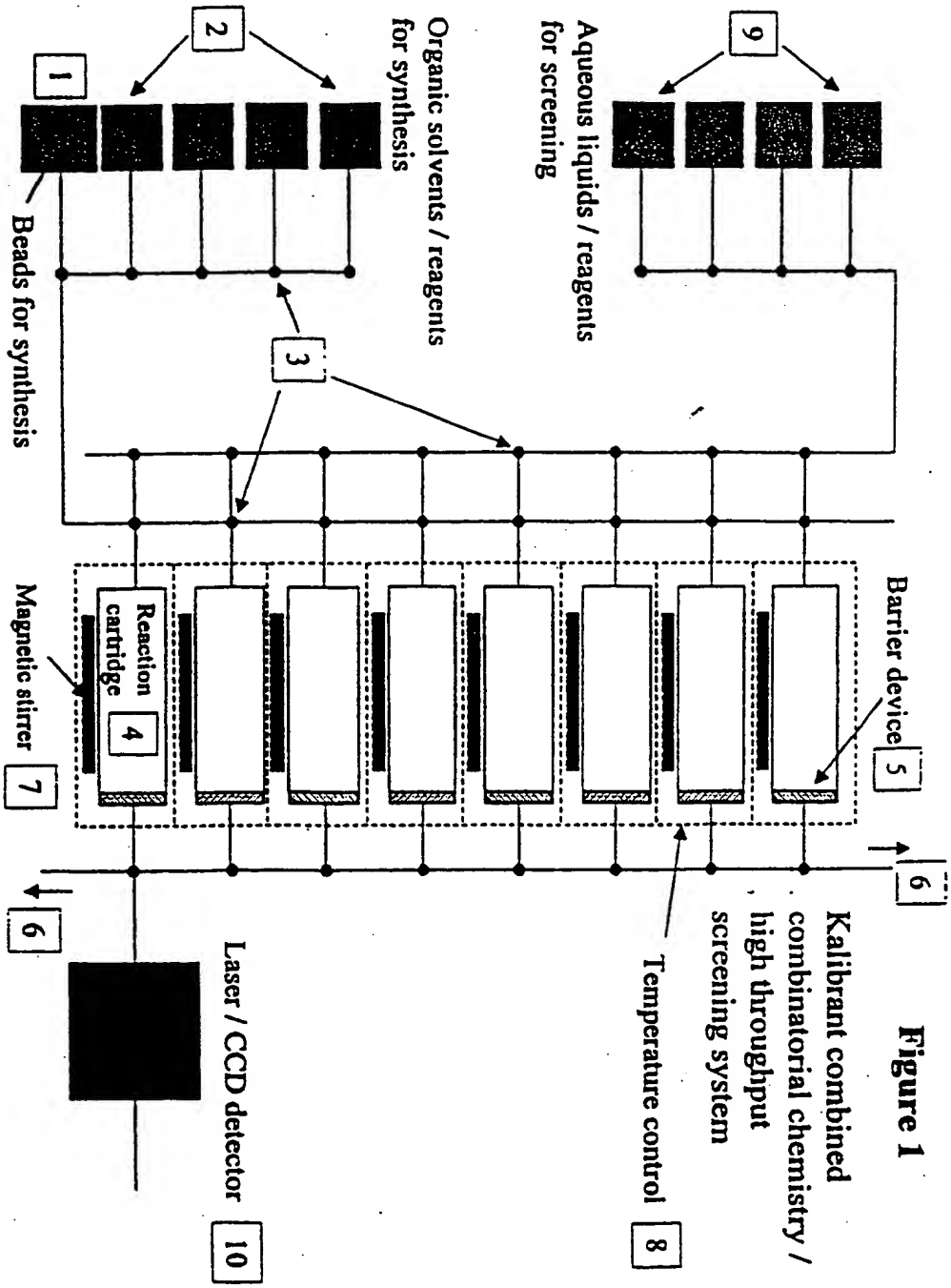
Aqueous liquids / reagents for screening
Organic solvents / reagents for synthesis
Beads for synthesis
Barrier device
Reaction cartridge
Magnetic stirrer
Temperature control
Laser / CCD detector
Kalibrant combined combinatorial chemistry / high throughput screening system
1
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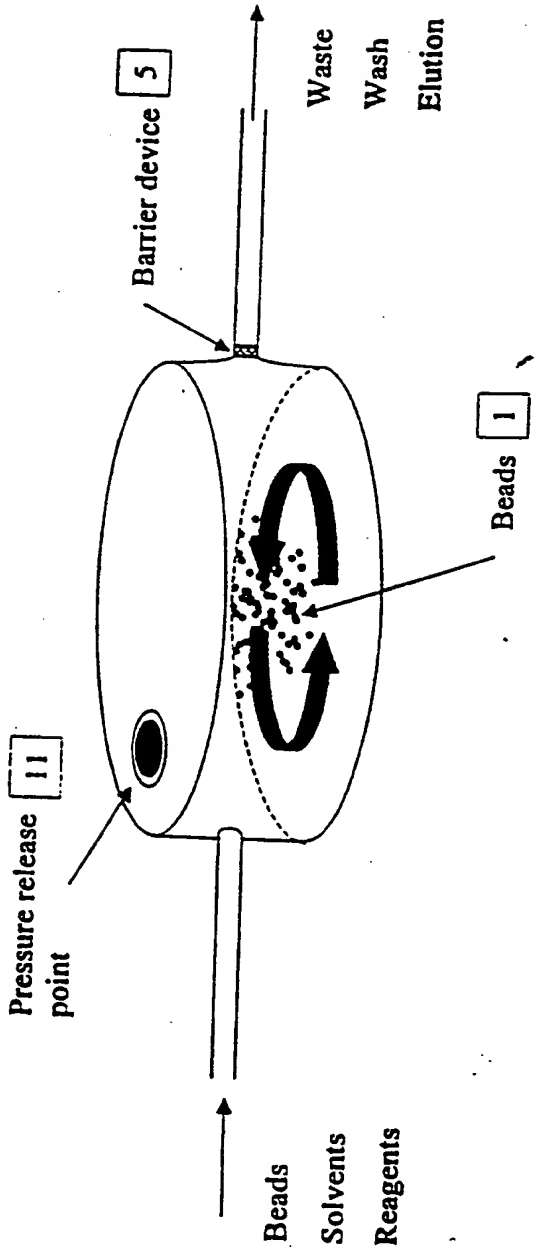
Figure 1

Figure 2

Combiscreen reaction cartridge [4]



INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 98/03761

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 85 01224 A (HOSSAIN H. SANEII) 28 March 1985 see abstract see page 7, line 24 - page 10, line 32 see page 12, line 13 - page 14, line 5 see page 21, line 25 - page 23, line 11 see page 37, line 8 - line 22 see page 46, line 12 - line 23 see page 47, line 23 - page 48, line 12 see figures 2,2A,3,4,6	1-6, 10-14, 17,18, 20-22
A		7-9,15, 16,19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 April 1999	22 04 99

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk	

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 98/03761

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with inc · ·n,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 07126 A (HYBRIDON, INC.) 27 February 1997 see page 7, line 15 - page 8, line 36 see page 10, line 19 - page 12, line 14 see figures 1,2	1,6,10
A		2-5,7-9, 11-22
X	WO 97 06884 A (PHARMACIA BIOTECH AB) 27 February 1997 see page 6, line 28 - page 14, line 14 see figures	1,6,10
A		2-5,7, 11-22
A	EP 0 794 001 A (THE PERKIN-ELMER CORPORATION) 10 September 1997 see the whole document	1-22
A	WO 91 17823 A (PROTOS CORPORATION) 28 November 1991 see page 8, line 13 - page 20, line 31 see figures	1-22
A	WO 95 12608 A (AFFYMAX TECHNOLOGIES N.V.) 11 May 1995 cited in the application	1-22
A	FR 2 630 928 A (RHÔNE POULENC CHIMIE, S.A.) 10 November 1989	

INTERNATIONAL SEARCH REPORT

Int. tional application No.
PCT/GB 98/03761

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 23-25
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
PCT Rule 6.2 (a).

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter inal Application No
PCT/GB 98/03761

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